PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 31508P WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/B 03/03487	International filing date *(day/month/year)* 02.07.2003	Priority date *(day/month/year)* 02.07.2002
International Patent Classification (IPC) or both national classification and IPC C07K16/30		
Applicant ONCOMAB GMBH et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
28.01.2004	22.10.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Covone-van Hees, M.G Telephone No. +31 70 340-4416

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB 03/03487

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-61 as originally filed

Sequence listings part of the description, Pages

1-10 received on 31.10.2003 with letter of 31.10.2003

Claims, Numbers

1-110 as originally filed

Drawings, Sheets

1/17-17/17 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1,3,5,6,8,10-12,46,47,51,52,68-95,108-110(part), 4,9,15-18,20,21,24-27,32-39,42-45,49,50,58-67100-107(complete)

   because:

   ☒ the said international application, or the said claims Nos. 77-90 (as for IA) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1,3,5,6,8,10-12,46,47,51,52,68-95,108-110 (part) 4,9,15-18,20,21,24-27,32-39,42-45,49,50,58-67,100-107 (complete)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1,3,5,6,8,10-12,46,47,51,52,68-95,108-110 (part) 2,7,13,14,19,22,23,28-31,40,41,48,53-57,96-99(complete) .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-3,6-8,13,14,19,22,23,28-31,40,41,48,53-57,69,70,74-76,80-83,87-90,93-99,108,109
	No:	Claims	5,10-12,46,47,51,52,68,71-73,77-79,84-86,91,92,110
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-3,5-8,10-14,19,22,23,28-31,40,41,46-48,51-57,68-99,108-110
Industrial applicability (IA)	Yes:	Claims	1-3,5-8,10-14,19,22,23,28-31,40,41,46-48,51-57,68-76,91-99,108-110
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1 The applicant is reminded that examination will be carried out only on the subject-matter covered by the first invention.

2 Claims 77-90 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV

Lack of unity of invention

The IPEA agrees and maintains the objection of lack of unity (Rule 13.1 PCT) raised by the ISA.

The application lacks unity for the following reason:

A priori the common linking technical feature of the polypeptides according to the claims (aa seq.ID 1,3; 5,7; 9,11 and disclosed in the description as PM1, PM2 and CM2 respectively), may be seen as the binding to neoplastic cells and not to non neoplastic cells, inducing apoptosis in the neoplastic cells.

However, at the priority date of the present application the concept of polypeptides having these characteristics and properties, namely to induce apoptosis in neoplastic cells to which they binds but not in non-neoplastic cells to which they do not bind, is known in the art.

Vollmers et al. (1998) exemplify in their publication a way to induce apoptosis of tumoral cells by means of a human monoclonal antibody (mAb) specifically binding to tumoral but not to non-tumoral cells. Said mAb has been isolated from patient with gastric cancer, is of IgM isotype and binds to a membrane protein of 50kD (see abstract; pg.35 right-hand column lines 13-19; pg.37 left-hand column lines 1-4,47-50).

The objective remaining problem of the application is the provision of alternative polypeptides having said characteristics and properties. The solution is the provision of the above mentioned three polypeptides.

As no other technical feature can be distinguished which, in the light of the prior art, could be regarded as special technical feature on which an unifying concept for the present inventions could be based, there is no single inventive concept underlying the claimed inventions of the present application.

The requisite unity of invention (Rule 13.1 PCT) does no longer exist. Reference is made to the search report for the subject-matter of the different inventions.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Examination of the 1st invention

claims: 1,3,5,6,8,10-12,46,47,51,52,68-95,108-110 (part);
2,7,13,14,19,22,23,28-31,40,41,48,53-57,96-99 (complete) and subject-matter: a purified polypeptide that binds to and induces apoptosis of neoplastic cells and does not bind to non-neoplastic cells. The polypeptide is coded by DNA sequences seq.ID 2 and 4, has amino acid sequences seq.ID 1 and 3, binds to the neoplastic cells ASPC-1 and BXPC-3. Related cells expressing the polypeptide and a method of generating these cells, a vector comprising said DNA and a cell comprising this vector, methods for the treatment and diagnosis of neoplasm.

1 **CITATIONS**

Reference is made to the following documents:

D1: VOLLMERS H P ET AL: "APOPTOSIS OF STOMACH CARCINOMA CELLS INDUCED BY A HUMAN MONOCLONAL ANTIBODY" CANCER, AMERICAN CANCER SOCIETY, PHILADELPHIA, PA, US, vol. 76, no. 4, 1995, pages 550-558, ISSN: 0008-543X

D2: WO 01/83560 A (ICHIKAWA KIMIHISA ;KIMBERLY ROBERT P (US); KOOPMAN WILLIAM J (US);) 8 November 2001 (2001-11-08)

D3: BRAENDLEIN STEPHANIE ET AL: "Characterization of five new fully human monoclonal IgM antibodies isolated from carcinoma patients" PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL, vol. 43, March 2002 (2002-03), page 970, 93rd Annual Meeting of the American Association for Cancer Research;San Francisco, California, USA; April 06-10, 2002, March, 2002 ISSN: 0197-016X

2 **NOVELTY** (Art. 33(2) PCT)

2.0.1 D1 studies the induction of apoptosis in stomach cancer cells by means of human monoclonal antibodies (mAb) specifically binding to tumoral and not to non-tumoral cells. Human antibodies are obtained from gastric cancer patients by fusion of spleen lymphocytes to an heteromyeloma cell line (see abstract and pg.551 left-hand column third paragraph). Purified human mAb are isolated using liquid chromatography (see pg.551-552 section "Antibody Purification"). Said mAb effectively inhibit tumour cell proliferation in vitro and in vivo inducing apoptosis (see tab.1, fig.3, pg.556 left-hand column third paragraph) and may

prove useful tools to treat cancer (see abstract).

2.0.2 In view of the disclosure of D1 the subject-matter of claims 5,10,11,46,47,51,52,68,77-79,84-86,91 is not new (Art. 33(2) PCT).

2.1.1 D2 discloses the production of a humanized mAb (and fragments thereof), binding only to tumoral and not to non-tumoral cells. Present mAb inhibits tumoral cell proliferation inducing apoptosis and can be used in medicaments to treat or diagnosis tumours (see pg. 5 lines 20-27, pg.16 lines 14-24, pg.20 lines 1-8, ex.7). The humanized mAb is produced by cloning the vector encoding the humanized heavy and light chain into host cells (see ex.18,19) and subsequent purification (see ex.20).

2.1.2 D2 is detrimental to the novelty of the subject-matter of claims 5,10-12,46,51,52,68,71-73,77-79,84-86,91,92,110 (Art. 33(2) PCT).

2.2.1 D3 summarizes the characterization of human mAb isolated from patients with carcinomas of colon, pancreas and lung useful as therapeutic agents. All bind only to malignant tissues. The mAb isolated from patients with colon carcinomas inhibits cell proliferation and induces apoptosis (see the whole abstract).

2.2.2 D3 anticipates the subject-matter of claims 5,10,11,46,47,51,52,68,77-79,84-86,91 which is therefore not new (Art. 33(2) PCT).

2.3 Summing up: the present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 5,10-12,46,47,51,52,68,71-73,77-79,84-86,91,92,110 is not new in the sense of Article 33(2) PCT.

3 **INVENTIVE STEP** (Art. 33(3) PCT)

3.1 The subject-matter of independent claim 1 contravenes the requirements of Art. 33(3) PCT. Said claim refers to a purified polypeptide that induces apoptosis of a neoplastic cell to which it binds, but does not induce apoptosis of a non-neoplastic cell and having the properties of binding to ASPC-1 and BXPC-3. It is unlikely, and the applicant fails to show, that all polypeptides having said binding properties also induces apoptosis. Consequently the polypeptide according to claim 1 does not solve the problem posed by the claim, namely to induce apoptosis, and does not comply with the requirements of Art.33(3) PCT.

3.2 The same reasoning applies, mutatis mutandis, to the subject-matter of the corresponding independent claim 6.

3.3 The subject-matter of independent claims 28-31 refers to a polypeptide, which is according to the description and examples an antibody, comprising one amino acid sequence (either seq. ID 1 or seq. ID 3). Said definition comprises not only the antibody disclosed in the application, but an unlimited range of antibodies, which not

necessary have the properties of inducing apoptosis and therefore do not solve the problem posed by the application (Art. 33(3) PCT).

3.4 The same reasoning applies, mutatis mutandis, to the subject-matter of the independent claims 53,55,96,98 (disclosing the corresponding nucleic acid).

3.5 The document D1 is regarded as being the closest prior art to the subject-matter of claims 40 and 41. D1 discloses the concept of the induction of apoptosis by means of human mAb specifically binding to neoplastic cells and which do not induce apoptosis in non-neoplastic cells. Said mAb is isolated from patients with stomach cancer (see also 2.0.1). The subject-matter of claims 40 and 41 differs in that the specific purified polypeptide binds to ASPC-1 and BXPC-3 (pancreatic carcinoma cell lines). The problem to be solved by the present invention may therefore be regarded as providing alternative human mAb. The solution proposed, namely human mAb which binds to ASPC-1 and BXPC-3, cannot be considered as involving an inventive step (Art. 33(3) PCT) since the polypeptide according to claims 40 and 41 appears to be merely an equivalent alternative to the human mAb available in the prior art, not leading to any surprising effects or advantages (Art. 33(3) PCT).

3.6 The same arguments cited for claims 40 and 41 are valid, mutatis mutandis, for the subject-matter of related product claims 57 and claims 93-95 (disclosing the corresponding nucleic acid) of the application.

3.7 Since the polypeptide per se does not comply with the requirements of Art.33(3) PCT, the subject-matters of claims 69,70 (methods to generate cells), claim 108 (vector) and claim 109 (cell comprising the vector) are also not inventive, being merely routine methods and/or products in this technical field.

3.8 Dependent claims 2,3,7,8,13,14,19,22,23,48,54,56,74-76,80-83,87-90, 97,99 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step, since they either do not solve the problem posed by the application (i.e. polypeptides comprising only one of the two amino acid sequences (either seq. ID 1 or seq. ID 3),) or they are mainly standard methods and products in this technical field, which fall within the routine skills of those in the art, and which do not appear to lead to any surprising effects or advantages.

3.9 For the assessment of the present claims 77-90 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a

known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.